

- in 2*
and
- (1) 5'-GAAGTCAAGGACACCGAGGAA-3'
 - (2) 5'-AGCCCTCTGGCCAGTCCTAGTG-3'.
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REMARKS

Reconsideration of this application as amended is requested.

Claims 1-8 are in this application. Claims 1, 2, 5, 6 and 8 have been amended.

Applicants affirm the provisional election of Group I, claims 1-8.

The specification is objected to under 35 U.S.C. 112, first paragraph as failing to accurately teach how to make and use the invention. The Applicants are little confused by this objection since the detailed description tells how the procedure is performed and Example 1 provides a specific example and conditions for the performance of the methods claimed. Thus, Applicants request reconsideration of this objection to the specification.

Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph. Applicants assert that the application of the methods can be used for any sequence once the sequence is known. Claim 2 has thus been amended so that it is only applicable to known sequences. Claims 2-5 and 7 are dependent directly or indirectly on Claim 1 and thus contain all of its restrictions. Thus, the procedure no longer is non-enabling. The Applicants assert that they shouldn't be restricted to those sequences which are currently known but rather the method is applicable to any sequence which becomes known in the future. Thus, although it might take undue experimentation to determine any specific sequence, it would not take undue experimentation to apply the method once the sequence is known. Thus, Applicants respectfully request that the rejection to claims 1-5 and 7 under 35 U.S.C. 112, first paragraph be withdrawn.

Claims 1-8 are rejected under 35 U.S.C., 103 as being unpatentable over Kogan, et al. As shown on the attached affidavit Kogan, et al is not prior art to this application. The application was filed within one year of Kogan and the invention was made before the Kogan publication. Applicants, therefore, request withdrawal of this rejection.

Even if Kogan was applicable, Applicants assert that Kogan, et al. only shows a PCR amplification procedure that has partially successfully amplified two sequences at once. Although Kogan, et al. refer to the possibility of doing other sequences simultaneously they were unable to adequately perform this analysis. It should be pointed out that to do two sequences at once does not require much significant modification of the PCR methodology, however in order to amplify greater than two sequences requires strict modification of the reaction conditions to achieve reliable and interpretable data. For example looking at Kogan, et al., Figure 1, there are clearly many extra bands from spurious amplification products that would prevent meaningful data interpretation when one amplifies more than two sequences at once. Furthermore, Kogan does not teach how to achieve amplification of at least three sequences. For example, the present application was the first to recognize and show that: (1) all the primers need to be composed of similar GC base compositions and lengths; (2) more enzyme than one normally adds to a PCR reaction is required; (3) longer extension times, up 8-fold the normally utilized are required; and (4) the number of PCR cycles performed must be optimized to have a profound effect on the interpretability and reliability of the reactions.

Claims 1, 2, 5, 6 and 8 have been amended to reflect the inventive step is simultaneous amplification of at least three sequences. This significantly differs from the Kogan, et al. procedure where amplification of three or more sequences would not be reliable or interpretable.

Additionally, Kogan, et al., were dealing with a different type of sequence, i.e., they were attempting to amplify repetitive DNA sequences rather than unique DNA

sequences. The primers utilized by Kogan, et al. were to amplify repetitive DNA which is present at hundreds of copies per chromosomes. The present invention amplifies unique DNA relative to the rest of the genome with a specificity and sensitivity sufficient for prenatal diagnosis of disease. Not only are the problems of amplifying these different types of DNA different, Kogan, et al. were not successful in their attempts and thus do not teach a method of multiplex PCR for unique sequences. As pointed out in the legend to their Figure 3B, they did not achieve their goal of specific amplification of their expected fragment, but also, obtained a large smear of spurious amplification products. Thus, although Kogan, et al. claimed specific amplification, they were not able to provide any reliable, interpretable amplification or to show the feasibility of a practical multiplex PCR or deletion detection for non-repetitive DNA.

In light of the amendments to the claims and the remarks, herein, Applicants respectfully request that the rejection based on 35 U.S.C. 103 be withdrawn.

Claims 1-5 are rejected under 35 U.S.C. 102a as being clearly anticipated by Kogan, et al. In light of the affidavit, Kogan, et al. is not a proper reference. Even if Kogan is a proper reference, as described above, it does not anticipate nor teach the present invention. Applicants respectfully request that the 35 U.S.C. 102(a) rejection be withdrawn.

Applicants are submitting an additional Combined Declaration and Power of Attorney. The original Combined Declaration of Power of Attorney lacked the signature of Charles Thomas Caskey. The Combined Declaration and Power of Attorney being submitted contains the original signature of Charles Thomas Caskey.

Applicants are also submitting an information disclosure statement with references and PTO Form PTO-1449 (modified).

If any additional fees are due please withdraw such fees from Account No. 06-2375 of which the undersigned is authorized to draw.

The affidavit, amendments and remarks provided should demonstrate that the specification is enabling and that there is adequate invention to support patentability. Accordingly, it is respectfully submitted that Kogan, et al is not a proper reference and even if it were a proper reference claims 1-8 are not obvious over Kogan, et al and are not anticipated by Kogan, et al. Thus, applicants respectfully request reconsideration of the rejections to Claims 1-8 in view of the amendments and remarks.

Applicants assert that the application is now in condition for allowance. If, however, any issues remain, the Examiner is requested to contact the undersigned at (713) 651-5325 and discuss the resolution of the outstanding issues.

Respectfully submitted,



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